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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,809	04/08/2004	Suketu P. Sanghvi	P0453.70116US01	9063

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EXAMINER	
SPIVACK, PHYLLIS G	
ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/821,809	SANGHVI ET AL.	
	Examiner	Art Unit	
	Phyllis G. Spivack	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-114* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-112 and 114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :6/24/04;8-9-04;12/13/04;2-23-07.

A Preliminary Amendment filed August 30, 2004 is acknowledged. Claim 113 is canceled. Claims 1-112 and 114 are presented and represent all of the claims under consideration.

A Response filed February 15, 2007 to a Request for Elections of Species is acknowledged. Applicants have elected senna as a laxative, docusate as a stool softener and methylnaltrexone as a peripheral opioid antagonist.

Accordingly, claims 1-112 and 114, wherein the elected species set forth *supra* are, respectively, the laxative, stool softener and peripheral opioid antagonist, in pharmaceutical formulations and methods of use, represent the subject matter presently under consideration. Other laxatives, stool softeners and peripheral opioid antagonists in the instant methods and compositions are withdrawn from consideration by the Examiner, as drawn to non-elected inventions. Re-affirmation of the elections is requested when Applicants respond to this Office Action.

Four Information Disclosure Statements filed June 24, 2004, August 9, 2004, December 13, 2004 and February 23, 2007 are further acknowledged. The references have been reviewed to the extent a publication date has been provided and are presented in the English language.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 48-112 and 114 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 99 and 100 of copending Application No. 11/441395. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the co-pending application are directed to pharmaceutical compositions comprising methylnaltrexone and at least one additional pharmaceutical agent that may be a laxative or stool softener.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 41 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The term "needleless injection" in claim 41 is confusing.

Clarification is required.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-112 and 114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pappagallo, M., The American Journal of Surgery, in view of Yuan et al., Anesthesia & Analgesia, Foss et al., Anesthesia & Analgesia and Cooper et al., U.S. Patent 6,455,537.

Pappagallo teaches the gastrointestinal effects of opioid analgesic therapy, such as treatment with morphine or codeine, in both cancer and noncancer patients experiencing either acute, as post-operative, or chronic pain. Opioid bowel dysfunction (OBD), usually described as constipation, is the most common and often most debilitating side effect reported by patients receiving opioid therapy. Within the central nervous system mu-receptors are the primary receptors involved in pain management. Pappagallo states overwhelming evidence supports the theory that peripheral mu-receptors have a dominant role in the development of OBD. In the periphery, stimulation of the mu-receptors affect a variety of gastrointestinal functions, such as motility, secretion, absorption and blood flow. The effects of opioids on the gut also are partly a result of their ability to accumulate in the intestinal tissue and have a direct local effect on the bowel. Opioid-induced effects affect both gastrointestinal tone, such as decreased stomach emptying and inhibition of both small and large intestine motility, as well as fluid content of the stool, and correlate with specific clinical manifestations of OBD. See Table 1, page 12S.

Pappagallo teaches opioid users require some type of laxative treatment, and stool softeners and stimulant-type laxatives are preferred. See the last paragraph on page 13S. Both docusate sodium and the stimulant laxative senna are preferred agents in the treatment of opioid-induced constipation. See the paragraph bridging columns one and two and Table 5 on page 15S. Further, in column one on page 16S, Pappagallo teaches the oral administration of quaternary opioid antagonists that have limited systemic absorption, do not readily cross the blood-brain barrier and are able to selectively antagonize the gastrointestinal effects of systemic opioids. The addition of a methyl group at the amine in the ring of naltrexone increases the polarity of the compound and decreases its lipid solubility. When given in combination with an opioid analgesic, such as morphine, methylnaltrexone (MNTX) prevents or reverses opioid-induced gastrointestinal effects, such as constipation, without interfering with analgesia. Methylnaltrexone, the quaternary N-methyl derivative of noroxymorphone has a local effect and elicits laxation without causing withdrawal symptoms in patients receiving acute or chronic opioid therapy.

As required by instant claims 2, 8, 14 and 20, Pappagallo suggests certain patients have experienced a less than optimal, or non-effective, result with prior laxative therapy, such that preventive strategies for patients receiving opioids is highly desired. See column one, page 14S.

Pappagallo fails to disclose optimal dosages or dosage forms for a peripheral opioid antagonist, a laxative or a stool softener. However, with respect to these claimed parameters in the instant compositions and methods of use, it is not inventive to

discover the optimum or workable dosage regimens by routine experimentation when general conditions of a claim are disclosed in the prior art. See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233,235 (CCPA 1955) and MPEP 2144.05(II). The determination of the optimum dosage regimen to employ with the presently claimed active agents and dosage forms would have been a matter well within the purview of one of ordinary skill in the art. Such determination would have been made in accordance with a variety of factors. These would have included such factors as the age, weight, sex, diet and medical condition of the patient, severity of the disease, the route of administration, pharmacological considerations, such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered a part of a drug combination. Thus, in the absence of evidence to the contrary, the currently claimed specific dosage amounts and dosage regimens are not seen to be inconsistent with the dosages that would have been determined by the skilled artisan.

Yuan teaches oral doses of 6.4 and 19.2 mg/kg and an IV dose of 0.45 mg/kg. Foss teaches enteric-coated methylnaltrexone wherein some drug release occurs in the stomach, as well as the lower gastrointestinal tract. Enteric-coated dosage forms are well established in the prior art for their ability to permit release of a quantity of drug at a particular section of GI tract in order to prevent interaction with another drug or to prevent decomposition in the stomach. Cooper teaches formulations for rectal administration of opioid antagonists. Such dosage forms are well within the purview of

those skilled in the art of formulation chemistry through no more than routine experimentation. See the bottom of column 8.

Therefore, in view of the teachings of Pappagallo, one skilled in the gastroenterology art would have been motivated to prepare a pharmaceutical formulation comprising a peripheral opioid antagonist and either a laxative or stool softener with a reasonable expectation of treating constipation in both cancer and noncancer patients, or for treating a condition that requires treatment with a laxative or stool softener, who are receiving opioid analgesic therapy. As a peripherally restricted opioid antagonist, methylnaltrexone normalizes bowel function in patients receiving opioids without affecting pain control. Pappagallo teaches the administration of laxatives prophylactically and throughout opioid therapy to improve bowel movements, and thus provides motivation to prepare formulations comprising the stimulant laxative senna or the stool softener docusate sodium, both of which are preferred agents in the treatment of OBD, together with methylnaltrexone. A kit is no more than a conventional packaged collection of related material.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phyllis G. Spivack whose telephone number is 571-272-0585. The examiner can normally be reached on 10:30 AM-7 PM.

If attempts to reach the examiner by telephone are unsuccessful after one business day, the Examiner's supervisor, Ardin Marschel, can be reached on 591-272-

0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Phyllis Spivack

Phyllis G. Spivack
Primary Examiner
Art Unit 1614

PHYLLIS SPIVACK
PRIMARY EXAMINER

May 27, 2007